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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FULBRIGHT & JAWORSKI L.L.P.
SUITE 2400
600 CONGRESS AVENUE
AUSTIN, TX 78701

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,877	MUKHOPADHYAY ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8,10,11,13-63,65-74,76-160,163,166,168 and 171-175* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,10,13-19, 21-29,76,77, 83-97 and 99-106* is/are rejected.

7)☒ Claim(s) *20 and 98* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 4-8,11,30-63,65-74,78-82,107-160,163,166,168 and 171-175.

Response to the Amendment

The Amendment filed on 4/28/2006 in response to the previous Non-Final Office Action (11/16/2005) is acknowledged and has been entered.

Claims 2-8, 10-11, 13-63, 65-74, 76-160, 163, 166, 168, 171-175 are currently pending.

Claims 4-8, 11, 30-63, 65-74, 78-82, 107-160, 163, 166, 168 and 171-175 are withdrawn from consideration as being drawn to a non-elected invention and/or species.

Claims 2-3, 10, 13-29, 76-77 and 83-106 are currently under consideration.

The Declaration filed on 4/28/2006 under 37 CFR 1.131 has been considered but is ineffective to overcome the Camden (US Patent No. 6,262,093) reference.

The Camden reference is a U.S. patent or U.S. patent application publication of a pending or patented application that claims the rejected invention or an obvious variant. An affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention or are obvious variants, see MPEP § 608 and 2306. If the reference and this application are not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the reference and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 76, 83-97 and 99-106 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in view of Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18).

Camden teaches (column 11, line 69 to column 12, line 51) a method of inducing apoptosis in cancer cells expressing abnormal p53 by administering an effective amount of a benzimidazole derivative. The patent further teaches (column 12, line 52 to column 13, line 24) a method of treating a patient having cancer expressing abnormal p53 by administering an effective amount of a benzimidazole derivative to induce apoptosis. Moreover, Camden discloses (column 14, line 53 to column 24, line 31) a method of treating a patient with cancer comprising administering an effective amount of a benzimidazole derivative. With regards to the cancer, the patent teaches that cancer includes, but is not limited to, cancers of the breast, lung, non-small cell lung and sarcoma (column 3, lines 45-50) or cancer that has survived treatment with another anticancer agent (column 29, lines 9-13). Specifically, Camden discloses the apoptotic effect in cancer cells such as, for example, MCF7 breast cells both in vitro (column 12, lines 46-51) and in vivo (column 16, lines 48+). With regards to the cancer cells, the patent teaches (column 12, lines 46-51) that some of the cancer cell lines tested are known to express abnormal p53. With regards to administration, Camden provides that 1 to 1000 mg/kg of a benzimidazole derivative (column 5, line 58 to column 6, line 17) can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor (column 6, lines 26-43). In addition, Camden teaches that the compound can be administered as a single daily dose or repeated at least once (column 6, lines 18-25). Furthermore, the patent shows that even at a concentration less than 10 μg/mL, the benzimidazole derivatives were capable of inducing apoptosis in p53 abnormal cell lines (column 12, lines 46-51). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Camden does not teach determining the tumor suppressor status by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdoma *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdoma *et*

al. further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Camden teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 (column 12, lines 52+), while Perdoma *et al.* teaches that the "response to cisplatin *in vivo* of tumors derived from different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdoma *et al.* teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

In response to this rejection, Applicants contend that Camden is not prior art because Applicants have demonstrated reduction to practice of the claimed invention before the priority date of Camden I, conceived of their invention before the priority date of Camden, and were diligent to the time of the priority date of the instant application as evidenced by the three declarations under 37 CFR 1.131. As such, the rejection of claims 76, 83-97 and 99-106 under 35 USC 103 cannot be sustained.

These arguments have been carefully considered, but are not found persuasive because, as noted above, an affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. As such, claims 76, 83-97 and 99-106 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in view of Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18).

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 76-77, 83-97, 99-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in view of Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) in further view of Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515).

Camden in view of Perdoma et al. teach, as applied to claims 76, 83-97 and 99-106 above, method of treating cancer by inducing apoptosis to a cell expressing abnormal p53 comprising administering a benzimidazole derivative. Moreover, the combination teaches determining the p53 status prior to the administration of a benzimidazole derivative.

Camden in view of Perdoma et al. does not teach that the benzimidazole derivative is mebendazole.

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that in mice with Ehrich carcinoma mebendazole inhibited tumor growth and increased survival time (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour *et al.* in the method taught by Camden in view of Perdoma. One would have been motivated to make these modifications because as evidenced by Delatour *et al.*, benzimidazole derivatives such as mebendazole have been shown to inhibit tumor growth. Thus, one of ordinary skill in the art would have a reasonable expectation of success that using mebenzdazole as taught by Delatour *et al* in the method taught by Camden in view of Perdoma, one would achieve an additional benzimidazole derivative that induces apoptosis in cells and tumors expressing abnormal p53.

New Rejections upon Reconsideration:

It is noted that Applicants have brought to the Examiner's attention that cancelled dependent claims 22 and 100 were never included in the previous rejection as being anticipated by or obvious over "Camden II" alone or in combination with any of the references cited. However, the claims that further depended from cancelled claims 22 and 100 were included. As such, it appears that the Examiner mistakenly did not include cancelled claims 22 and 100, and therefore, the "new" rejections are set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) as evidenced by Camden (US Patent 6,262,093, 1999) in view of Perdoma et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) *of record.*

Camden teaches a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). With regards to administration, Camden teaches (column 5, lines 1-10) that the benzimidazole derivatives can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor. Although Camden does not specifically teach that the administration of benzimidazole induces apoptosis, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Camden (US Patent 6,262,093, 1999), the administration of benzimidazole derivatives results in apoptosis (see column 11, line 65 to column 12, line 51). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC

2001). Moreover, while Camden does not explicitly characterize the tumor cell lines as expressing a tumor suppressor gene such as p53, the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 64, Table 4) that A459 tumor cells express wild-type p53. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Hence, even though the claims are drawn to a mechanism by caner cells are inhibited, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Camden does not teach determining the tumor suppressor status by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdoma *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdoma *et al.* further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Camden teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 (column 12, lines 52+), while Perdoma *et al.* teaches that the "response to cisplatin *in vivo* of tumors derived from

different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdoma *et al.* teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

Claims 3 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in view of Perdoma et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) *of record* in further view of either of Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515) of record or Nasr *et al.* (Journal of Pharmaceutical Sciences 1985; 74: 831-836).

Camden in view of Perdoma et al. teach, as set forth above for claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106, a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). Moreover, the combination teaches determining the p53 status prior to the administration of a benzimidazole derivative.

Camden in view of Perdoma et al. does not teach that the benzimidazole derivative is mebendazole.

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that a method of inhibiting tumor growth in mice comprising administering the benzimidazole derivative, mebendazole (abstract).

Nasr *et al.* teach (page 831, paragraph bridging 1st column and 2nd) *in vivo* anticancer activity correlation of aromatic, aliphatic, and heterocyclic carbamates and their thio-isosters against both intraperitoneally implanted murine P-388 lymphocytic leukemia and L-1210 lymphoid leukemia. Specifically, the reference teaches anticancer activity of benzimidazole carbonates (page 834, Table VIII and page 835, 2nd column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to inhibit tumor growth because each of the benzimidazole derivatives disclosed by the references have close structural similarities and similar

utilities. In the instant case, the courts have held that "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (see in MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on close structural similarity of chemical compounds. See also MPEP § 2144.08, paragraph II.A.4.(c). Thus, one of skill in the art would have a reasonable expectation of success that by substituting a benzimidazole derivate as taught by Delatour et al. or Nasr et al. in the method of Camden in view of Perdoma et al., one would achieve a method of inhibiting the growth of cancer.

Claims 13-14 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 5,880,144, 1999) in view of Perdoma et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) *of record* in further view of Lucci et al. (Cancer; 86:300-311, published online on November 2000).

Camden in view of Perdoma et al. teach, as set forth above for claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97 and 100-106, a method of killing lung tumor cells (A-549), breast tumor cells (MCF-7) and colon tumor cells comprising administering a benzimidazole derivative (column 6, lines 64 to 67, and column 7, Table 3). The patent further teaches a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer (abstract). Moreover, the combination teaches determining the p53 status prior to the administration of a benzimidazole derivative.

Camden in view of Perdoma et al not teach that the tumor cell is a multidrug resistant tumor cell, wherein the tumor cell is a breast tumor cell.

Lucci et al. teach multidrug resistance modulators and doxorubicin synergize to elevate ceramide levels and elicit apoptosis in drug-resistant cancer cells, specifically drug resistant human breast cancer cells lines. Moreover, the reference teaches that multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances (page 300, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a multidrug resistant cell line, such as a breast cancer cell, in the method

taught by Camden in view of the teachings of Lucci et al. One would have been motivated to do so because as taught by Lucci, multidrug resistance is a formidable roadblock to the effective treatment of cancer by conventional chemotherapy, wherein the resistance complicates treatment in many instances. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a benzimidazole derivative to multidrug resistant cell, one would achieve a method of inhibiting tumor growth in a patient that has already become resistant to conventional chemotherapy.

Note: Claim 20 and 98 are objected to as being dependent from a rejected independent claim.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER